

**POSTOPERATIVE ANALGESIA AFTER CARDIAC SURGERY-~~AN OPEN-LABEL~~
~~DOUBLE-BLIND~~,A DOUBLE-BLIND PROSPECTIVE AND RANDOMIZED
COMPARISON OF WOUND INFILTRATION WITH LIPOSOMAL BUPIVACAINE
AND BUPIVACAINE HYDROCHLORIDE**

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Executive Summary

Moderate to severe pain is common in up to 75% of patients undergoing sternotomy for cardiac surgery and 4% of them develop chronic post-sternotomy pain¹. Pain after cardiac surgery is multifactorial and caused by skin incision, sternotomy, sternal retraction, internal mammary artery dissection, mediastinal and pleural drains, saphenous vein harvest, position of the patient and stretching of brachial plexus. Pain after cardiac surgery is often undertreated because of fear of inducing cardiorespiratory depression in otherwise compromised patients. Untreated and undertreated pain has severe adverse consequences in cardiac surgical patients. Inadequate pain control can lead to increased sympathetic discharge, increased myocardial demand, myocardial ischemia, cardiac arrhythmias, decreased ventilator effort and clearance of secretions, prolonged mechanical ventilation, increased postoperative pulmonary complications, delayed patient mobilization, poor patient satisfaction, increased length of intensive care unit and hospital stay and increased cost of health care¹. Commonly used treatment modalities include acetaminophen, oral opioids, non-steroidal anti-inflammatory drugs and intravenous opioids. Opioids are used sparingly because of fear of side effects namely excessive sedation, respiratory depression (hypoxemia and carbon-dioxide retention), prolonged ileus, constipation, urinary retention and postoperative nausea and vomiting. Neuraxial anesthesia and analgesia (spinal, epidural and paravertebral blocks) are avoided in cardiac surgery due to the risk of inducing neuraxial hematoma with anticoagulation and neurological deficits. Neuraxial catheters also need management by specialized acute pain service teams. Current practice of local anesthesia infiltration into the wound is limited by the short duration of action of available local anesthetic drugs (lidocaine and bupivacaine) and was associated with increased incidence of wound

infections². Recent studies explored the use of liposomal bupivacaine (Exparel; Pacira Pharmaceuticals, Inc., Parsippany, NJ) and duration of analgesia with this slow release bupivacaine preparation may last up to 72 hours. Liposomal bupivacaine produced significant analgesic benefit in hemorrhoidectomy, bunion surgery, total joint arthroplasties, arthroscopic surgery, breast implantations and abdominal surgical procedures³. There are no studies to date that investigated the use of liposomal bupivacaine in cardiac surgical population. Our aim is to study the analgesic efficacy and safety of wound infiltration with liposomal bupivacaine in patients undergoing cardiac surgery with sternotomy and cardiopulmonary bypass (CPB) and compare it with bupivacaine hydrochloride infiltration.

Background

Liposomal bupivacaine (LB) has recently been the target for many clinical trials with the expectation that long lasting analgesic efficacy would improve patient satisfaction and patient outcomes. Several randomized studies have shown positive effect on postoperative pain relief with the use of LB (Table 1). The following evidence-based research indicates the utility of LB in specific surgical populations.

Abdominal surgery

Kalogera et al⁴ in a retrospective cohort study examined the utility of wound infiltration with LB after gynecologic surgery through laparoscopy and laparotomy. Median oral morphine equivalents, IV patient controlled analgesia (IVPCA) opioids requirements, IV rescue analgesia with opioids and opioid related side effects were significantly reduced with LB in their enhanced recovery after surgery (ERAS) population. Efficacy was better in laparoscopy population than in laparotomy patients.

Hutchins et al⁵ in a randomized observer blinded study compared ultrasound guided transversus abdominal plane (TAP) blocks with LB versus non-liposomal bupivacaine for analgesia after laparoscopic hand assisted donor nephrectomy. There was a significant decrease in maximal pain scores and IVPCA fentanyl injection up to 72 hours after injection in LB group. The same research group in another prospective randomized observer blinded study evaluated the use of subcostal TAP injection using bupivacaine and LB for patients undergoing robotic assisted hysterectomy⁶. There was decrease in maximal pain scores, opioid consumption as well as decreased incidence of PONV with liposomal TAP blocks for first 72 hours after surgery. A trend was noted in the LB group towards a shorter hospital stay duration. Beck et al⁷ compared patients receiving multimodal analgesia that included LB infiltration and patients using conventional pain management using IV opioids in their ERAS program for major colorectal surgery. Patients receiving multimodal analgesia had lower pain scores, lower IV opioid consumption, decreased opioid related side effects and decreased length of hospital stay.

In spite of many impressive studies showing positive effects of LB in acute pain management of abdominal surgery, a few others failed to show significant benefit. Knudson et al⁸ compared LB and bupivacaine hydrochloride for wound infiltration in colorectal surgery in a non-sponsored, prospective randomized and double blinded clinical trial (n=57). IVPCA hydromorphone requirements were comparable for both groups and they suggested larger clinical trials to define the effectiveness of LB. In another cohort study using propensity- matched analysis, TAP block with LB was compared with IVPCA and epidural analgesia in patients undergoing major abdominal surgery (106 patients in each group). TAP block was non-inferior to epidural block and was comparable to IVPCA in terms of pain scores⁹. They recommended a larger clinical trial comparing these techniques. Knight et al¹⁰ in a prospective, randomized, patient blinded clinical

trial evaluated wound infiltration with LB and bupivacaine hydrochloride for postoperative analgesia after urologic surgery. No difference was found between the groups in pain scores, opioid consumption, adverse events or length of hospital stay.

Failure to demonstrate analgesic benefit in the above mentioned studies could be related to sample size, study methods (prospective versus retrospective cohort), variation in wound infiltration method and LB volumes, type of surgery (laparotomy versus laparoscopy), other analgesics used and duration of follow up.

Orthopedic surgery

Shoulder surgery

Routman et al¹¹ studied the effect of adding LB infiltration to multimodal analgesia (consisted of narcotics, gabapentin, non-steroidal anti-inflammatory drugs, acetaminophen and single injection interscalene block) on postoperative analgesia and duration of hospital stay. The LB cohort had fewer narcotic requirements, better visual analog scores and shorter hospitalization after shoulder arthroplasty. However, when local infiltration with LB was compared with interscalene block in a prospective randomized clinical trial, no significant benefits could be demonstrated with the use of LB infiltration¹².

Knee arthroplasty

A systematic review conducted by Kuang et al¹³, of studies comparing standard periarticular injections and LB injections have shown that LB had comparable length of stay, ambulation distance, PONV, pain scores and narcotic consumption after total knee arthroplasty (TKR). Considering the cost, they questioned the use of LB in pain management after TKR. Ma et al¹⁴

published another systematic review of 6 clinical trials comparing femoral nerve block and LB injection and found that pain scores were comparable with both techniques but narcotic consumption was lower with LB. Adverse events were similar with both groups.

Hip Arthroplasty

Yu et al¹⁵ compared standard pain management (n=686) to LB infiltration (n=586) in total hip arthroplasty (THR) patients. Pain scores were similar. Patients who received LB had lower narcotic consumption, better achievement of physical therapy milestones, decreased length of hospital stay and improvement in disposition to home. Barrington et al reported several large series of arthroplasty patients treated with LB and demonstrated superior pain relief with better outcomes using this drug^{16,17,18}.

Spine surgery

Puffer et al¹⁹ studied the analgesic efficacy of LB infiltration and compared with standard IV narcotic analgesia in patients undergoing single level discectomy procedures. Patients in LB group received shorter duration of IV analgesics (average difference 10.3 hours) but no differences in pain scores, total narcotic consumption or length of stay were detected when compared to standard pain management group. Kim et al studied LB infiltration versus standard bupivacaine infiltration in patients undergoing unilateral interbody lumbar fusion. They demonstrated significantly reduced opioid consumption, reduced pain scores and length of hospital stay in their patients who received LB infiltration²⁰. In patients undergoing posterior spinal decompression, Grief et al²¹ compared standard bupivacaine and LB infiltration and found no statistically significant difference in pain scores, narcotic consumption and length of hospital stay. However, there was a trend towards less narcotic consumption in LB group.

Plastic surgery

Several studies evaluated the use of LB and demonstrated its benefits in plastic surgical procedures such as breast reconstruction, augmentation mammoplasty, abdominal wall reconstruction, mastectomy, bunionectomy and abdominoplasty²²⁻²⁶. Vyas et al²⁷ performed a systematic review of 160 studies and found eight studies comparing LB and standard pain relief techniques (nerve blocks, epidural analgesia, patient controlled analgesia and IV narcotics). They reported safety, tolerability and equivalent or better efficacy with LB in plastic surgery.

Cardiothoracic surgery

Very few clinical trials examined the role of LB in postoperative analgesia after cardiac surgery. Thoracotomy is associated with significant pain and inadequate pain relief may lead to poor outcomes. Epidural analgesia is commonly used to treat post thoracotomy pain but is associated with hypotension, respiratory depression, pruritus and need for acute pain service consult (for infusion pumps management and follow-up). Intercostal block with LB was tested and compared with epidural analgesia in a retrospective study by Khalil et al²⁸. There was a significant improvement in pain scores on days 1 and 3 but no significant difference on day 2. No significant difference could be shown in narcotic consumption but there was significant decrease in pulmonary complications in LB group. Total length of hospital stay was less in LB group.

Robotic cardiac surgery with multiple thoracic ports and incisions can be associated with significant postoperative pain. Balkhy et al²⁹ compared bupivacaine (n=30) and LB (n=30) infiltration through incision and port sites in patients undergoing robotic cardiac surgery. Patients in LB group had less pain intensity, reduced narcotic consumption and reduced incidence of PONV

compared to bupivacaine group. The results did not achieve statistical significance because of small sample size but there was a trend towards better analgesic efficacy with LB.

There are no studies to date on the use of LB infiltration and its analgesic efficacy in cardiac surgery done through sternotomy. Although other surgical approaches are useful in selected group of patients and surgeries, majority of cardiac surgery is still done through sternotomy approach. We hypothesize that a randomized clinical trial to evaluate the benefits of LB infiltration in cardiac surgery will be beneficial for this surgical population.

Specific Aims

1. To study the analgesic efficacy and safety of sternal wound infiltration with liposomal bupivacaine on postoperative analgesia in patients undergoing elective cardiac surgery with cardiopulmonary bypass
2. To study the effect of wound infiltration with liposomal bupivacaine on functional patient recovery, patient satisfaction, chronic sternal pain and composite complications after elective cardiac surgery
3. ~~To study the cost effectiveness of liposomal bupivacaine in elective cardiac surgery~~

Research Design

Trial Design

Study design will be a prospective, randomized and ~~double-blinded~~ ~~open-label~~ ~~double-blind~~ clinical trial. The study will include patients over 18 years of age undergoing cardiac surgery with sternotomy approach at University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

Recruitment

Potential participants will be screened by the cardiac surgeons and study coordinators at the preoperative/surgical clinics or the day before surgery for inpatients. They will be asked for their interest in participating in a research study related to pain control ~~after~~ before their cardiac surgery

Randomization Process

Participating patients will be randomized by computer generated random numbers to either the bupivacaine or liposomal bupivacaine group.

Eligibility Criteria

Inclusion:

Patients over the age of 18

Male or Female

All races

Open cardiac surgery through sternotomy approach (eg. coronary artery bypass graft, valvular heart procedures, and other open cardiac procedures along with coronary artery bypass)

Surgery with the use of cardiopulmonary bypass

Exclusion

Minimally invasive heart surgery through thoracotomy approach

~~Patients receiving regional analgesia such as intrathecal morphine~~

Patients undergoing procedures under deep hypothermic circulatory arrest

Patients with active infections such as infective endocarditis

Emergency surgery

Patients undergoing transplantations and ventricular assist device insertion

Patients on any mechanical circulatory support preoperatively

Patient's refusal

End stage liver or renal disease

Allergy to bupivacaine

Patients who cannot understand the study procedure or refuse to participate

Redo-sternotomy

Participation in another study

Patients with severe right or left ventricular dysfunction (EF <25%)

Patients requiring chronic opioids for chronic pain conditions

Treatment Groups

Patients will be randomized to Liposomal bupivacaine or Bupivacaine group.

At the end of surgery, infiltration of the sternotomy wound and mediastinal /chest tube sites will be done by one of the two methods. Wound infiltration will be done on both sides of the wound from subcutaneous space till periosteum. Injection will be done approximately at 20 cc per inch of sternotomy wound.

Group 1; Liposomal bupivacaine 20 cc (266 mg) + Bupivacaine Hydrochloride 0.25% 40 cc (100 mg) + made up to calculated volume with normal saline solution based on length of the incision and the number of chest tubes (20cc per tube and 20cc per inch of incision).

Group 2; Bupivacaine 0.25% 2 mg/kg not to exceed 150 mg – made up to calculated volume with normal saline solution based on length of the incision and the number of chest tubes (20cc per tube and 20cc per inch of incision).

Anesthetic Management

After the patient signs informed consent, patients are enrolled into the study. Midazolam 1-2 mg IV premedication will be administered in the holding area or in the operating room before arterial line placement. Induction of anesthesia method and medications are not standardized and will be decided by the anesthesiologist. After intubation, oxygen and a volatile anesthetic (isoflurane or sevoflurane) will be used for maintenance of anesthesia and muscle paralysis achieved with non-depolarizing muscle relaxants titrated to neuromuscular monitor. Intermittent fentanyl will be administered to all patients as analgesic and will be titrated by anesthesia care team

During CPB, isoflurane will be administered through CPB circuit and neuromuscular paralysis is maintained. Bispectral index is monitored to keep the values between 40-60. Additional Midazolam is administered during rewarming or any other period if BIS is higher than 60. Higher BIS can also be managed with increasing the concentration of inhalational agent if tolerated. Additional vasopressors or vasodilators are administered and inotropes initiated as required by the anesthesia care team. Sevoflurane is preferred for post bypass period in view of extubating patients in the operating room or early in the intensive care unit. During post CPB period, ondansetron 4 mg IV will be administered to all patients in both groups. IV hydromorphone 1 mg will be administered for all patients during sternal wiring. After the drapes come down, patient's neuromuscular blockers will be reversed and extubation performed in the operating room. Patients who could not be extubated will be transferred on propofol to intensive care unit and will be extubated shortly by the ICU staff.

Outcomes

Postoperative pain scores and total narcotic consumption in the first 72 hours postoperative period will be co-primary outcomes. Pain intensity will be evaluated by numeric rating scale, NRS (0- no pain 10- worst pain) at rest, deep inspiration or cough and at movement. NRS scores will be evaluated every 4 hours for 24 hours, every 8 hours for 48 hours and every 12 hours for 72 hours.

Rescue post-operative analgesia will be provided by intravenous or oral acetaminophen, non-steroidal anti-inflammatory drugs, oral oxycodone (5-10mg), IV narcotics administered by the nurse and patient controlled analgesia (PCA) with narcotics based on the patient's ability to take oral drugs and the intensity of pain. Three commonly used IV narcotics include: hydromorphone, morphine and fentanyl. All narcotics administered in the first 72 hours will be converted to total IV morphine equivalent for comparison between the two groups.~~Patient-controlled postoperative analgesia with hydromorphone (0.2 mg every 6 minutes) without a basal infusion will be primarily used during ICU stay. Intravenous hydromorphone (0.2-0.4 mg) will be administered by nurses before starting on IVPCA or if IVPCA was ineffective. Oral oxycodone and IV acetaminophen can be given as rescue analgesics. All IV and oral narcotics administered in the first 72 hours will be converted to IV morphine equivalent for the purpose of analysis. IVPCA is discontinued if pain scores were persistently less than 4 and duration of IVPCA requirement will be noted.~~

Secondary outcome measures include the time to extubation, time to mobilization and out of bed to chair, time to oral intake, noninvasive ventilation requirement and re-intubations, use of incentive spirometry, postoperative nausea and vomiting, major organ dysfunction (cardiac, renal, respiratory and central nervous system) from Society of Thoracic Surgeon's database, length of hospital and ICU stay, readmissions and 30 day and in hospital mortality.

Other pre-specific outcome measures include: Delirium, patient satisfaction, chronic pain assessment, and serum cortisol levels.

An Intensive Care Delirium Screening Checklist (ICDSC) will be administered at baseline, 48 hours and 72 hours post-operatively. The participant will also be assessed for patient satisfaction regarding pain management at the time of discharge. Chronic pain assessment using 0–10 Numeric Pain Rating Scale Questionnaire (for both groups): Two follow-up questionnaires will be administered to all study subjects at 6 and 12 months after the surgery. Subjects will be asked: On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain? Current, worst and best pain levels will be questioned and an average pain score will be taken during rest and activity.

In addition to clinical parameters, the suppression of stress response will be evaluated by comparing the hormone levels between the groups. Serum cortisol hormone levels will be measured at baseline (right before surgery), 8, 48 and 72 hours postoperatively.

Sample Size and statistics

Based on our previous institutional study, the estimated average narcotic consumption in the first 48 hours after sternotomy was (IV morphine equivalent doses) 27 mg (SD 18 mg). Based on our previous institutional study, the estimated average narcotic consumption in the first 48 hours after sternotomy was (IV morphine equivalent doses) 27 mg (SD 18 mg). We anticipate mean narcotic consumption to be reduced to 14 mg with the use of wound infiltration with liposomal bupivacaine. With Alpha at 0.05 and 80% power, we estimate 30 patients will be required in each group (total n=60 patients). Since cardiac surgical patients may have high drop out rate (15%), we plan to recruit 70 patients to demonstrate the analgesic superiority (total narcotic consumption in 48 hours)

of liposomal bupivacaine infiltration. ~~We anticipate 30% reduction in narcotic consumption with the use of wound infiltration with liposomal bupivacaine. With Alpha at 0.05 and 80% power, we estimate 51 patients will be required in each group (total n=102 patients). Since cardiac surgical patients may have high drop-out rate (15%), we plan to recruit 1187 patients to demonstrate the analgesic superiority (total narcotic consumption in 48 hours) of liposomal bupivacaine infiltration. Interim statistical analysis will be done at the end of 50 patients before proceeding with a complete study.~~

Data will be collected on demographic variables (age, gender, weight) and procedural variables (type of surgery, duration of surgery, CPB duration) and postoperative outcome parameters. Continuous variables such as narcotic consumption, length of ICU and hospital stay, and time to extubation will be analyzed using Student t test or Mann Whitney U test wherever appropriate. Incidence of complications and other binary variables between the groups will be analyzed by Chi Square test or Fisher exact test. P value less than 0.05 will be considered significant. Confidence intervals and relative risks will be defined wherever appropriate. Intention-to-treat analysis will be used for the study population.

Study Timeline and Milestones

This study will be conducted over one year starting from the enrollment of the first patient. Proposed timeline for the trial is given below:

OBJECTIVE	PROPOSED TIMELINE
Secure funding and ethical approvals	May 201 8 ⁷
Write protocol, design forms, and create database	complete
Assemble and train study team	May 201 8 ⁷ – June 201 8 ⁷
Recruit participants	June 201 8 ⁷ – July 201 9 ⁸
Monitor initial study compliance and safety	November 201 8 ⁷
Interim Analysis for DSMB	December 201 8 ⁷
Meet with DSMB for Monitoring	Every month meeting
Final Study result analysis	August 201 9 ⁸
Abstract presentation	ASA October 201 9 ⁸
Study ends with manuscript submission	October 201 9 ⁸

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Table 1

Study	Study design	Surgery	Groups	Primary outcome	Results
Gorfine et al (2011)	RCT Multicenter (n=189)	Hemorrhoidectomy	Liposomal bupivacaine (LB) 300 mg in 30 cc NS versus Placebo	NRS	Pain scores and opioid use were significantly less with LB
Smoot et al (2012)	RCT (n=136)	Mammoplasty	Liposomal bupivacaine 300 mg versus bupivacaine HCL 200 mg	NRS	No difference in pain scores but opioid consumption was less with LB
Golf et al (2011)	RCT (n=193)	Bunionectomy	Liposomal bupivacaine 180 mg versus placebo	NRS	Significant differences in opioid use and pain scores with LB
Bramlett et al (2012)	RCT (n=134)	Total knee arthroplasty	Multiple doses of LB (dose- response) vs bupivacaine	NRS	No difference in pain scores opioid consumption between groups